Welcome to **HIV this month**! In this issue, we cover the following topics:

1. **Reduce sexual transmission**
   - Transient increase in HIV shedding from male circumcision wounds
   - South African students support HIV testing in schools
   - Alcohol and ART do not mix – but how to get the message across?

2. **Prevent HIV among drug users**
   - Multiple harms faced by Azerbaijani prisoners

3. **Eliminate new HIV infections among children**
   - Better retention in care among HIV-exposed infants whose mothers receive combination ART

4. **15 million accessing treatment**
   - Negative HIV antibody test results among children living with HIV
   - Literacy and technology experience are predictors of a successful mHealth programme

5. **Avoid TB deaths**
   - High early mortality after ART initiation despite screening for TB and cryptococcal disease
   - Screening for and treating cryptococcal infection – better evidence of impact necessary
   - Hepatitis B virus co-infection: a challenge to successful ART in sub-Saharan Africa?

6. **Close the resource gap**
   - Community-based services strengthen the continuum of care and are cost-effective
   - Economic strengthening programmes for people living with HIV may increase their quality of life

7. **Eliminate gender inequalities**
HIV and sexuality curricula programmes that address gender or power are five times more effective than those that do not.

8. Strengthening HIV integration

- Need for further water, sanitation and hygiene programmes among people living with HIV

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Peter Godfrey-Faussett and Celeste Sandoval
UNAIDS
1. Reduce sexual transmission

HIV shedding from male circumcision wounds in HIV-infected men: a prospective cohort study.


Background: A randomized trial of voluntary medical male circumcision (MC) of HIV-infected men reported increased HIV transmission to female partners among men who resumed sexual intercourse prior to wound healing. We conducted a prospective observational study to assess penile HIV shedding after MC.

Methods and findings: HIV shedding was evaluated among 223 HIV-infected men (183 self-reported not receiving antiretroviral therapy [ART], 11 self-reported receiving ART and had a detectable plasma viral load [VL], and 29 self-reported receiving ART and had an undetectable plasma VL [<400 copies/ml]) in Rakai, Uganda, between June 2009 and April 2012. Preoperative and weekly penile lavages collected for 6 wk and then at 12 wk were tested for HIV shedding and VL using a real-time quantitative PCR assay. Unadjusted prevalence risk ratios (PRRs) and adjusted PRRs (adjPRRs) of HIV shedding were estimated using modified Poisson regression with robust variance. HIV shedding was detected in 9.3% (17/183) of men not on ART prior to surgery and 39.3% (72/183) of these men during the entire study. Relative to baseline, the proportion shedding was significantly increased after MC at 1 wk (PRR = 1.87, 95% CI = 1.12-3.14, p = 0.012), 2 wk (PRR = 3.16, 95% CI = 1.94-5.13, p < 0.001), and 3 wk (PRR = 1.98, 95% CI = 1.19-3.28, p = 0.008) after MC. However, compared to baseline, HIV shedding was decreased by 6 wk after MC (PRR = 0.27, 95% CI = 0.09-0.83, p = 0.023) and remained suppressed at 12 wk after MC (PRR = 0.19, 95% CI = 0.06-0.64, p = 0.008). Detectable HIV shedding from MC wounds occurred in more study visits among men with an HIV plasma VL > 50 000 copies/ml than among those with an HIV plasma VL < 400 copies/ml (adjPRR = 10.3, 95% CI = 4.25-24.90, p < 0.001). Detectable HIV shedding was less common in visits from men with healed MC wounds compared to visits from men without healed wounds (adjPRR = 0.12, 95% CI = 0.07-0.23, p < 0.001) and in visits from men on ART with undetectable plasma VL compared to men not on ART (PRR = 0.15, 95% CI = 0.05-0.43, p = 0.001). Among men with detectable penile HIV shedding, the median log10 HIV copies/milliliter of lavage fluid was significantly lower in men with ART-induced undetectable plasma VL (1.93, interquartile range [IQR] = 1.83-2.14) than in men not on ART (2.63, IQR = 2.28-3.22, p < 0.001). Limitations of this observational study include significant differences in baseline covariates, lack of confirmed receipt of ART for individuals who reported ART use, and lack of information on potential ART initiation during follow-up for those who were not on ART at enrollment.

Conclusion: Penile HIV shedding is significantly reduced after healing of MC wounds. Lower plasma VL is associated with decreased frequency and quantity of HIV shedding from MC wounds. Starting ART prior to MC should be considered to reduce male-to-female HIV transmission risk. Research is needed to assess the time on ART required to decrease shedding, and the acceptability and feasibility of initiating ART at the time of MC.

Abstract Full-text [free] access
**Editor’s notes:** Voluntary medical male circumcision (VMMC) decreases the heterosexual acquisition of HIV, herpes simplex virus type 2 and human papillomavirus (HPV) in men. There are also benefits for female partners. Among men living with HIV, VMMC reduces genital ulcer disease and HPV, but it does not reduce the risk of HPV transmission. Further, VMMC increases HIV transmission to female partners among people who engage in sex before wound healing, though not among couples who delay resumption of sex. Men living with HIV may seek VMMC for multiple reasons, and WHO guidelines state that they should not be denied the service if they request it. Despite counselling to abstain from sex until full wound healing, a substantial proportion of men resume sex before this. In this cohort study among HIV-positive men in Uganda, the authors found that penile HIV shedding had a transient increase after VMMC, peaking in the second week after VMMC. By 6 to 12 weeks after surgery, when wounds had healed, HIV shedding was lower than pre-surgery. There was no change in plasma viral load during the study. Among men with HIV shedding, the lowest quantities of shedding were observed among men on ART and with undetectable viral load. The authors highlight the potential role of ART to reduce the risk of HIV transmission following VMMC, for example by considering initiating ART prior to VMMC for men living with HIV, and encouraging adherence to suppress viral load. With current WHO guidelines, the majority of men living with HIV attending for VMMC will be eligible for ART, and VMMC could be a useful entry point for treatment although this may pose logistical challenges.

“Students want HIV testing in schools” a formative evaluation of the acceptability of HIV testing and counselling at schools in Gauteng and North West provinces in South Africa.


**Background:** The proposal by the South African Health Ministry to implement HIV testing and counselling (HTC) at schools in 2011 generated debates about the appropriateness of such testing. However, the debate has been between the Ministries of Education and Health, with little considerations of the students. The **main aim of the study was to assess the students’ opinions and uptake of HIV testing and counselling in general, and the acceptability of the provision of HIV testing and counselling in schools.** The study also determined the association between socio-demographic characteristics, sexual behaviour, and HIV testing behaviour of the students.

**Methods:** A survey was conducted among grade 10-12 high school students in North West and Gauteng provinces, South Africa. Seventeen high schools (nine rural and eight urban) were randomly selected for the administration of a researcher-assisted, self-administered, semi-structured questionnaire.

**Results:** A total of 2970 students aged 14-27 years participated in the study; 1632 (55%) were girls, 1810 (61%) ever had sex, and 1271 (49.8%) had more than one sex partner. The **mean age of first sexual activity was 15.6. Half (n = 1494, 50.1%) had been tested for HIV.** Having multiple sexual partners, age, and gender were significantly associated with increased odds of having had a HIV test. **Fear, being uninformed about HTC, and low HIV risk perceptions were the reasons for not getting tested.** The acceptability of HTC at school was high (n = 2282, 76.9%) and 2129 (71.8%) were willing to be tested at school. Appropriateness, privacy, and secrecy were the main arguments for and against HTC at school. One-third (n = 860, 29%) had intentions to disclose their HIV status to students versus 1258 (42.5%) for teachers. **Stigma, discrimination and secrecy were the primary reasons students did not intend to disclose.**

**Conclusions:** A high acceptability of HTC and willingness to be tested at school suggest that HIV prevention programs tailored to youth have a high potential of success given the
readiness of students to uptake HTC. Bringing HIV testing to the school setting will increase the uptake of HTC among youth and contribute towards efforts to scale up HTC in South Africa.

Abstract  Full-text [free] access

Editor’s notes: Strategies to promote HIV testing, the gateway to all prevention and treatment programmes, are continuously being developed and piloted with the goal of universal knowledge of HIV status. Adolescents, especially those first starting to have sex, are an important population for considering relevant, creative, and accessible testing programmes. This paper presents important insights into whether HIV testing would be acceptable in schools from the perspectives of the learners themselves. Researchers conducting this study in two provinces in South Africa found that only about half the adolescents they interviewed had ever tested, but most would be supportive of HIV tests available in their schools. Fear, lack of information, and risk perception were reasons for not having tested previously. It is possible that just the act of introducing testing to the schools would bring sufficient awareness and accessibility to increase testing rates. Further, it could also be an opportunity for learners to become more knowledgeable about their risk and safer sex practices. Important aspects of testing programmes within schools for consideration would be how to preserve and ensure confidentiality, as well as quality and contextual relevance of service delivery.

Qualitative study of changes in alcohol use among HIV-infected adults entering care and treatment for HIV/AIDS in rural southwest Uganda.


Alcohol has a substantial negative impact on the HIV epidemic in sub-Saharan Africa, particularly in Uganda, where heavy alcohol consumption is common. Using a content analytic approach, this qualitative study characterizes changes in alcohol use among 59 HIV-infected Ugandan adults (>18 years old), who reported any alcohol use in the previous year as they entered HIV care. Most participants reported attempting to cease or reduce alcohol intake over the study period. Reasons for decreased use included advice from clinicians, interference with social obligations, threats to financial security, and negative impact on social standing. Participants reported difficulty abstaining from alcohol, with incentives to continue drinking including desire for social inclusion, stress relief, and enjoyment of alcohol. These contrasting incentives created a moral quandary for some participants, who felt ‘pulled’ between ‘good’ and ‘bad’ influences. Results suggest brief interventions addressing self-identified obstacles to change may facilitate long-term reductions in drinking in this population.

Abstract  Full-text [free] access

Editor’s notes: The heavy consumption of alcohol may facilitate the risk of infection with HIV. Alcohol use can also affect adherence to antiretroviral therapy and may also have an impact on disease progression. This paper on alcohol use among people initiating antiretroviral therapy in Uganda is an important addition to the literature. As well as using in-depth interviews to gather information from people newly initiated on antiretroviral therapy, the research team also observed clinic consultations and other activities. As a result, the authors can describe in this paper the rather moralistic tone adopted by some counsellors who urged participants to stop drinking alcohol without really explaining why. This contrasted with information provided by clinicians on the risk of alcohol interfering with the absorption of medication; something that participants found much more persuasive. The authors describe the benefits as well as risks associated with alcohol use, noting that
These factors are very similar to challenges faced by general populations in other settings. This leads the authors to conclude that - motivational interviewing - an approach to alcohol use reduction which has proved successful in resource-rich settings could work in resource-limited settings like Uganda. Such programmes provide a way for participants to develop strategies to address obstacles to change, while receiving support from trained staff at the clinic. This paper not only provides valuable information from a well-designed study but also provides encouragement for the use of brief programmes in Africa.

2. Prevent HIV among drug users

Burden of substance use disorders, mental illness, and correlates of infectious diseases among soon-to-be released prisoners in Azerbaijan.


Background: Despite low HIV prevalence in the South Caucasus region, transmission is volatile. Little data are available from this region about addiction and infectious diseases among prisoners who transition back to communities.

Methods: A nation-wide randomly sampled biobehavioral health survey was conducted in 13 non-specialty Azerbaijani prisons among soon-to-be-released prisoners. After informed consent, participants underwent standardized health assessment surveys and testing for HIV, hepatitis B and C, and syphilis.

Results: Of the 510 participants (mean age=38.2 years), 11.4% were female, and 31.9% reported pre-incarceration drug injection, primarily of heroin. Prevalence of HCV (38.2%), HIV (3.7%), syphilis (3.7%), and HBV (2.7%) was high. Among the 19 HIV-infected inmates, 14 (73.7%) were aware of their HIV status, 12 (63.2%) were receiving antiretroviral therapy (ART), and 5 (26.3%) had CD4<350cells/mL (4 of these were on ART). While drug injection was the most significant independent correlate of HCV (AOR=12.9; p=0.001) and a significant correlate of HIV (AOR=8.2; p=0.001), both unprotected sex (AOR=3.31; p=0.049) and working in Russia/Ukraine (AOR=4.58; p=0.008) were also correlated with HIV.

Conclusion: HIV and HCV epidemics are concentrated among people who inject drugs (PWIDs) in Azerbaijan, and magnified among prisoners. A transitioning HIV epidemic is emerging from migration from high endemic countries and heterosexual risk. The high diagnostic rate and ART coverage among Azerbaijani prisoners provides new evidence that HIV treatment as prevention in former Soviet Union (FSU) countries is attainable, and provides new insights for HCV diagnosis and treatment as new medications become available. Within prison evidence-based addiction treatments with linkage to community care are urgently needed.

Abstract access

Editor’s notes: This is an important study describing prevalence of HIV, hepatitis B and hepatitis C among a prison population in Azerbaijan. The importance of the study stems from the need to monitor infections among a highly vulnerable population of prisoners. While the study does not report on current injecting drug use among the population, a third of the sample reported injecting drugs prior to their detention and will need support with their injecting drug use while in prison. This will include the provision of opioid substitution therapy and needle-syringe programmes. This study highlights the
vulnerability of prisoners to HIV, hepatitis B and hepatitis C and the need for harm reduction in prisons. At the same time, the study also highlights other adverse health outcomes relating to drug use or being in prison in terms of poor mental health outcomes among the sample. It illustrates an association between a measure of anxiety disorder and HIV infection. The strengths of this study lie in the large sample that were recruited from a broad range of prison facilities across the country, increasing the representativeness of the findings to all people living in prisons. Findings suggest an association between HIV infection and condomless sex, as well as a history of working in Russia and Ukraine. This suggests the potential for transmission of HIV across the region and points to the potential for sexual transmission of HIV in a region where transmission has been historically driven by injecting drug use. Findings contribute to the growing evidence for the urgent need for hepatitis C virus (HCV) treatment and increased access to needle-syringe programmes and opioid substitution therapy within prisons and communities in the region. The high adherence among prisoners to HIV treatment demonstrates the provision of HCV treatment to the population is entirely feasible. Previous evidence from Russia has illustrated the difficulties for prisoners in maintaining HIV treatment post-release and this study underscores the need for support to facilitate the integration of individuals into harm reduction programmes including HIV treatment in community settings post-release.

3. Eliminate new HIV infections among children

Maternal combination antiretroviral therapy is associated with improved retention of HIV-exposed infants in Kinshasa, Democratic Republic of Congo.


Background: Programs to prevent mother-to-child HIV transmission (PMTCT) are plagued by loss to follow-up (LTFU) of HIV-exposed infants. We assessed if providing combination antiretroviral therapy (cART) to HIV-infected mothers was associated with reduced LTFU of their HIV-exposed infants in Kinshasa, DR Congo.

Methods: We constructed a cohort of mother-infant pairs using routinely collected clinical data. Maternal cART eligibility was based on national guidelines in effect at the time. Infants were considered LTFU following three failed tracking attempts after a missed visit or if more than six months passed since they were last seen in clinic. Statistical methods accounted for competing risks (e.g. death).

Results: 1318 infants enrolled at a median age of 2.6 weeks (interquartile range [IQR]: 2.1-6.9), at which point 24% of mothers were receiving cART. Overall, 5% of infants never returned to care following enrollment and 18% were LTFU by 18 months. The 18-month cumulative incidence of LTFU was 8% among infants whose mothers initiated cART by infant enrollment and 20% among infants whose mothers were not yet on cART. Adjusted for baseline factors, infants whose mothers were not on cART were over twice as likely to be LTFU, with a subdistribution hazard ratio of 2.75 (95% confidence limit: 1.81, 4.16). The association remained strong regardless of maternal CD4 count at infant enrollment.

Conclusion: Increasing access to cART for pregnant women could improve retention of HIV-exposed infants, thereby increasing the clinical and population-level impacts of PMTCT interventions and access to early cART for HIV-infected infants.

Abstract access
Editor’s notes: An estimated one third of all HIV-exposed infants are lost to follow up (LTFU) by three months in sub-Saharan Africa. Regular follow-up of HIV-exposed infants is necessary to ensure that they are provided with prophylactic drugs, have an opportunity for early infant diagnosis, and if HIV-positive that they are started on combination antiretroviral treatment (cART) as soon as possible. This study using routinely collected programmatic data (2007 - 2013) in Kinshasa found that infants whose mothers had not yet initiated cART were more than twice as likely to be LTFU as infants whose mothers had initiated cART. An important point to highlight is that this study was unable to tease out what proportion of the effect of maternal cART on infant LTFU was attributable to reduction in infant mortality. There are few data on factors that contribute to LTFU in HIV-exposed infants. The available evidence suggests that structural barriers, including transport, waiting time and cost, affect retention in care.

4. 15 million accessing treatment

Young age at start of antiretroviral therapy and negative HIV antibody results in HIV-infected children when suppressed.


Background: Negative results on standard HIV antibody tests have been described among HIV-infected children suppressed on antiretroviral therapy (ART) started early in life. Here, we describe the frequency and predictors of this phenomenon in a well characterized cohort of treated children.

Methods: We selected samples from 103 HIV-infected children who started ART 14 months of age or less and from 122 children who started 6 months of age or less followed as part of two sequential clinical trials in Johannesburg, South Africa. Children had attained viral suppression on ART and had received ART for between 3 and 6.4 years (mean 4.3 years) when tested for HIV antibody using a standard ELISA (Genescreen HIV1/2 version 2; Bio-rad).

Results: Only children 6 months of age or less when ART was started had negative antibody results when tested after suppression on ART several years later. Negative or low-positive antibody results were observed in 40.0, 37.0 and 27.8% of children starting ART less than 2 months of age, or starting during month 2 or 3, respectively. This dropped to 5.9, 3.5 and 5.3% if ART was started during month 4, 5 and 6, respectively. Higher CD4 percentage prior to ART initiation and no recorded intermittent viremia also predicted negative antibody results.

Conclusion: Testing negative on standard HIV antibody tests occurs fairly commonly among HIV-infected children who started ART by 3 months of age or less and are virally suppressed. It would be prudent in clinical practice to avoid HIV antibody tests among virally suppressed, early-treated children to prevent unnecessary confusion.

Abstract access

Editor’s notes: After 18 months of age, HIV antibody tests are used routinely for diagnosis in children, as in adults, with the typical expectation that antibody status does not revert to negative after a positive result.
This study illustrated that 34% of HIV-positive children who had started antiretroviral therapy (ART) by three months of age and were virally suppressed at the time of antibody testing, tested HIV antibody negative and/or had low-positive antibody results when tested several years later.

Negative HIV antibody test results were strongly related to the age of starting ART. The proportion of children who had a negative antibody test result dropped to approximately 5% if they had started ART between three and six months of age. No negative HIV antibody tests were observed among children who started ART after six months of age. Several studies have illustrated that younger age at starting ART is associated with a reduced size of the viral reservoir, and that this may be associated with better longer term outcomes. Assuming that a negative antibody response indicates a smaller viral reservoir, these findings suggest that the benefit of immediate ART after diagnosis may be attenuated in children who start ART after three months of age.

Notably, a higher pre-treatment CD4 percentage was independently associated with a greater likelihood of a negative HIV antibody test. Given that ART is now recommended in infants regardless of clinical and immunological status, it is likely that there may be higher rates of antibody negativity than those reported in this study, as the study cohort started ART before universal treatment guidelines were implemented.

In a clinical setting, a negative HIV antibody test in a child treated with antiretroviral therapy will raise concern among clinicians and parents about whether the child was initially misdiagnosed with HIV infection. Indeed there have been anecdotal reports of healthcare workers stopping ART in children testing HIV antibody negative based on mistaken assumptions. Great attention should be paid to ensuring that the initial diagnosis prior to ART initiation in a child under 18 months of age is based on adequate virological tests. Use of HIV antibody tests in children who initiated ART under six months of age should be avoided, given the high chance of the test being falsely negative and the considerable potential for misinterpretation.

Know your audience: predictors of success for a patient-centered texting app to augment linkage to HIV care in rural Uganda.


Background: Despite investments in infrastructure and evidence for high acceptability, few mHealth interventions have been implemented in sub-Saharan Africa.

Objective: We sought to (1) identify predictors of uptake of an mHealth application for a low-literacy population of people living with HIV (PLWH) in rural Uganda and (2) evaluate the efficacy of various short message service (SMS) text message formats to optimize the balance between confidentiality and accessibility.

Methods: The trial evaluated the efficacy of a SMS text messaging app to notify PLWH of their laboratory results and request return to care for those with abnormal test results. Participants with a normal laboratory result received a single SMS text message indicating results were normal. Participants with an abnormal test result were randomized to 1 of 3 message formats designed to evaluate trade-offs between clarity and privacy: (1) an SMS text message that stated results were abnormal and requested return to clinic ("direct"), (2) the same message protected by a 4-digit PIN code ("PIN"), and (3) the message "ABCD EFG" explained at enrollment to indicate abnormal results ("coded"). Outcomes of interest were (1) self-reported receipt of the SMS text message, (2) accurate identification of the message, and (3) return to care within 7 days (for abnormal results) or on the date of the scheduled appointment (for normal results). We fit regression models for each outcome with the following explanatory variables: sociodemographic characteristics,
CD4 count result, ability to read a complete sentence, ability to access a test message on enrollment, and format of SMS text message.

Results: Seventy-two percent (234/385) of participants successfully receiving a message, 87.6% (219/250) correctly identified the message format, and 60.8% (234/385) returned to clinic at the requested time. Among participants with abnormal tests results (138/385, 35.8%), the strongest predictors of reported message receipt were the ability to read a complete sentence and a demonstrated ability to access a test message on enrollment. Participants with an abnormal result who could read a complete sentence were also more likely to accurately identify the message format (AOR 4.54, 95% CI 1.42-14.47, P=.01) and return to clinic appropriately (AOR 3.81, 95% CI 1.61-9.03, P=.002). Those who were sent a PIN-protected message were less likely to identify the message (AOR 0.11, 95% CI 0.03-0.44, P=.002) or return within 7 days (AOR 0.26, 95% CI 0.10-0.66, P=.005). Gender, age, and socioeconomic characteristics did not predict any outcomes and there were no differences in outcomes between those receiving direct or coded messages.

Conclusions: Confirmed literacy at the time of enrollment was a robust predictor of SMS text message receipt, identification, and appropriate response for PLWH in rural Uganda. PIN-protected messages reduced odds of clinic return, but coded messages were as effective as direct messages and might augment privacy.

Abstract  Full-text [free] access

Editor’s notes: The authors of this study tap into the increasingly widespread ownership of mobile phones, individually or shared, in sub-Saharan Africa to examine whether text message reminders can be used as a tool to help keep people in care. This randomised trial from rural Uganda adds to the large literature, largely from high-income settings, on the acceptability of SMS text message programmes among people living with HIV. It is the first to directly assess the impact of literacy and experience with technology on clinical outcomes. The study illustrated that confirmed literacy, the absence of a PIN-code protector, and a demonstrated ability to access a sample SMS text message were good predictors of an appropriate response to an SMS reminder. Further, factors such as educational attainment, income, age and gender were not associated with the outcomes. The results have important implications for future mHealth programmes focussed on low-literacy end-users, illustrating the need to assess literacy and technology experience before implementation.

5. Avoid TB deaths

Implementation and operational research: Integrated pre-antiretroviral therapy screening and treatment for tuberculosis and cryptococcal antigenemia.


Objective: To demonstrate the feasibility of integrated screening for cryptococcal antigenemia and tuberculosis (TB) before antiretroviral therapy (ART) initiation and to assess disease specific and all-cause mortality in the first 6 months of follow-up.

Methods: We enrolled a cohort of HIV-infected, ART-naive adults with CD4 counts ≤250 cells per microliter in rural Uganda who were followed for 6 months after ART initiation. All subjects underwent screening for TB; those with CD4 ≤100 cells per microliter also had cryptococcal antigen (CrAg)
screening. For those who screened positive, standard treatment for TB or preemptive treatment for cryptococcal infection was initiated, followed by ART 2 weeks later.

Results: Of 540 participants enrolled, pre-ART screening detected 10.6% (57/540) with prevalent TB and 6.8% (12/177 with CD4 count ≤100 cells/µL) with positive serum CrAg. After ART initiation, 13 (2.4%) patients were diagnosed with TB and 1 patient developed cryptococcal meningitis. Overall 7.2% of participants died (incidence rate 15.6 per 100 person-years at risk).

Death rates were significantly higher among subjects with TB and cryptococcal antigenemia compared with subjects without these diagnoses. In multivariate analysis, significant risk factors for mortality were male sex, baseline anemia of hemoglobin ≤10 mg/dL, wasting defined as body mass index ≤15.5 kg/m, and opportunistic infections (TB, positive serum CrAg).

Conclusions: Pre-ART screening for opportunistic infections detects many prevalent cases of TB and cryptococcal infection. However, severely immunosuppressed and symptomatic HIV patients continue to experience high mortality after ART initiation.

Abstract access

Editor’s notes: Early mortality remains high among people starting antiretroviral therapy (ART) in resource-constrained settings. The risk of death is strongly associated with low baseline CD4 count. Leading causes of death in this population include tuberculosis (TB) and cryptococcal disease.

ART-naïve people with CD4 counts of 250 cells/µl or less were included in this study at a district hospital in Uganda. All were offered screening for TB, and people with CD4 counts below 100 cells/µl also had screening for cryptococcal antigen with follow-on management for people screening positive. The TB screening protocol comprised symptom screening plus an initial sputum for smear microscopy and culture, and a second sputum for smear was taken if the first was negative. Further investigations appear to have been according to clinical presentation rather than standardised. Overall, 13.3% of participants were diagnosed with TB. Some 6.8% of people with CD4 below 100 cells/µl had a positive serum cryptococcal antigen test. One was diagnosed with and treated for cryptococcal meningitis and the other 11 were treated with high dose fluconazole.

Despite the high prevalence of TB and cryptococcal disease detected and treated, the overall mortality was 7.2% (39/540) by six months. This is a minimum estimate, since it assumes that the 33 additional people who were lost to follow-up, transferred or withdrawn were all alive at six months. The mortality rate was higher among people diagnosed with TB, and was very high among people who were cryptococcal antigen positive, despite fluconazole treatment. The article does not describe the care pathways in detail, so it is not clear whether there were delays in treatment initiation which could be reduced, for example if point-of-care diagnostic testing with immediate results had been available at enrolment. In addition there is no comparison group and so the effect of this package of care on mortality is not clear. However the results suggest that early mortality may remain substantial among people presenting with advanced HIV disease in the absence of even more intensive management.

Several trials are in progress to evaluate programmes aiming to reduce early mortality among people starting ART, including trials of empirical TB treatment (i.e. without bacteriological confirmation). In last month’s HIV This Month we featured a trial of a cryptococcal screen and treat programme plus community support which reduced 12-month mortality from 18% to 13%. The results of these trials will inform the optimal package of care for people presenting with low CD4 counts. Ultimately, earlier HIV testing and linkage to care would be the ideal way to reduce the high mortality among people starting ART with very low CD4 counts.
Cryptococcal antigen screening and early antifungal treatment to prevent cryptococcal meningitis: a review of the literature.


Background: Screening individuals with AIDS for serum cryptococcal antigen (CrAg), followed by treatment of CrAg positives with antifungals, may prevent cryptococcal meningitis. This review examined data on CrAg screening and treatment in resource-limited settings.

Methods: We searched articles published during 2007-2014 on the effectiveness and cost-effectiveness of CrAg screening and treatment on the outcomes of mortality, morbidity, retention in care, quality of life, and/or prevention of ongoing HIV transmission. We rated overall quality of individual articles, summarized the body of evidence, the expected impact, and cost-effectiveness for each outcome.

Results: We identified 2613 articles. Eight met all inclusion criteria. Five studies addressed mortality and/or morbidity outcomes; all were observational and had small sample sizes; 3 lacked a comparison group. Ratings of study quality ranged from "medium" to "weak," and the quality of the overall body of evidence for mortality and morbidity outcomes was rated as "fair." The intervention's expected impact on mortality and morbidity was rated as "moderate." The 4 cost-effectiveness studies included in the analysis showed that CrAg screening and treatment interventions are highly cost-effective. No studies addressed retention in care, quality of life, or HIV transmission.

Conclusions: Although limited, the body of evidence regarding CrAg screening and treatment suggests that the intervention may have an impact on preventing cryptococcal meningitis and death in persons with AIDS. Additional research is needed to quantify the intervention's effectiveness and identify optimal treatment dosing and implementation best practices.

Abstract access

Editor’s notes: This systematic review was one of a series aimed at evaluating the impact of services supported by the US President’s Emergency Plan for AIDS Relief (PEPFAR). The review set out to assess the evidence around the impact of targeted cryptococcal antigen (CrAg) testing and antifungal treatment for people with advanced HIV disease. In 2011 World Health Organization (WHO) gave a conditional recommendation, based on low quality evidence, that adults with CD4 count <100 cells per μL, in populations where the CrAg prevalence is above 3%, should undergo CrAg screening and be provided with antifungal treatment if CrAg positive.

The quality of the evidence was rated using a system adapted from the US Preventive Services Task Force. Five observational studies that evaluated the impact of the CrAg screening and antifungal treatment approach on mortality were included. Most of these did not have a comparator. One study used a historical control group from the same facility and another study compared mortality in people who received fluconazole following a positive CrAg, to people who did not. All studies had a very small number of deaths. In the five studies, mortality in people testing CrAg positive and receiving fluconazole varied between 0 and 29%. Based on these studies it would be difficult to evaluate the true impact of the strategy on mortality.

Four cost-effectiveness studies from different settings were also reviewed. All four studies suggested that a strategy with CrAg screening and antifungal treatment would be cost-effective. However, the cost-effectiveness modelling was based on data from the observational studies mentioned above and
required other assumptions based on low quality evidence, leading to substantial uncertainty around the cost-effectiveness estimates.

Although a few countries have already implemented CrAg screening and antifungal treatment strategies, better quality evidence is necessary to inform management more broadly in countries with a high burden of cryptococcal disease. Some evidence has already appeared, with a randomised controlled trial in Tanzania and Zambia demonstrating a reduction in mortality with a CrAg screening strategy combined with a community support package during the early phase of antiretroviral therapy (see HIV This Month Issue 4). In addition there are three other randomised controlled trials exploring the impact of CrAg screening, ongoing or planned in Uganda, Zimbabwe and Viet Nam (NCT01535469, NCT02434172, and NCT02334670). It is hoped that the evidence generated by these studies will improve our understanding of the impact of a CrAg screening strategy and also give further insight into how best to implement this in different health care settings.

Prevalence of HIV and hepatitis B virus co-infection in sub-Saharan Africa and the potential impact and program feasibility of hepatitis B surface antigen screening in resource-limited settings.


Background: Screening people living with HIV for hepatitis B virus (HBV) co-infection is recommended in resource-rich settings to optimize HIV antiretroviral therapy (ART) and mitigate HBV-related liver disease. This review examines the need, feasibility, and impact of screening for HBV in resource-limited settings (RLS).

Methods: We searched 6 databases to identify peer-reviewed publications between 2007 and 2013 addressing (1) HIV/HBV co-infection frequency in sub-Saharan Africa (SSA); (2) performance of hepatitis B surface antigen (HBsAg) rapid strip assays (RSAs) in RLS; (3) impact of HBV co-infection on morbidity, mortality, or liver disease progression; and/or (4) impact of HBV-suppressive antiretroviral medications as part of ART on at least one of 5 outcomes (mortality, morbidity, HIV transmission, retention in HIV care, or quality of life). We rated the quality of individual articles and summarized the body of evidence and expected impact of each intervention per outcome addressed.

Results: Of 3940 identified studies, 85 were included in the review: 55 addressed HIV/HBV co-infection frequency; 6 described HBsAg RSA performance; and 24 addressed the impact of HIV/HBV co-infection and ART. HIV/HBV frequency in sub-Saharan Africa varied from 0% to >28.4%. RSA performance in RLS showed good, although variable, sensitivity and specificity. Quality of studies ranged from strong to weak. Overall quality of evidence for the impact of HIV/HBV co-infection and ART on morbidity and mortality was fair and good to fair, respectively.

Conclusions: Combined, the body of evidence reviewed suggests that HBsAg screening among people living with HIV could have substantial impact on preventing morbidity and mortality among HIV/HBV co-infected individuals in RLS.

Abstract access

Editor’s notes: The routes of transmission for hepatitis B virus (HBV) and HIV are the same, and they frequently co-infect individuals in high HIV prevalence settings. HIV has also been shown to accelerate the progression of HBV. This has important implications for ART programmes, given also the potential for hepatotoxicity of ART. The response of both infections to certain antivirals gives an
opportunity to treat both infections simultaneously, but also the potential to engender resistant strains of virus if treatment is optimised for one and not the other.

This paper reviews the evidence that might support inclusion of HBV screening as part of HIV care programmes. No clinical trials have been done in this area, so the review is based on observational studies. The data are incomplete and geographically patchy, largely from Nigeria and South Africa. However, this does not prevent the authors from concluding that the co-infection risk is sufficiently high and the consequences of lack of treatment sufficiently severe to consider allocation of scarce resources to identify and manage HBV co-infection in HIV programmes. Appropriate validated screening tools (rapid tests for hepatitis B surface antigen) are available. The potential benefit warrants consideration of this issue in sub-Saharan Africa, and inclusion of HBV surveillance alongside HIV to resolve the paucity of data in most countries. This should be rapidly followed by further consideration of the cost- and risk-benefit of introduction of an HBV screening and treatment programme.

Interested readers might also refer to a review by Matthews et al. (J Clin Virol 2014;6:20-33) which considers similar questions and also discusses hepatitis C co-infection.

6. Close the resource gap

Cost-effectiveness of community-based strategies to strengthen the continuum of HIV care in rural South Africa: a health economic modelling analysis.


Background: Home HIV counselling and testing (HTC) has been shown to achieve high testing coverage and linkage to care compared to existing facility-based HTC, particularly among asymptomatic persons. This study evaluates the population-level health impact and cost-effectiveness of a community-based home HTC package in KwaZulu-Natal, South Africa.

Methods: We parameterized an individual-based model with data from home HTC and linkage field studies that achieved high coverage (91%) and linkage to ART (80%) in rural KwaZulu-Natal, South Africa. Costs were derived from a linked micro-costing study. The model simulated 10,000 individuals over ten years and incremental cost-effectiveness ratios (ICERs) were calculated for the intervention relative to the existing 'status quo' of facility-based testing, with costs discounted at 3% annually.

Findings: Implementing home HTC in addition to current practice is predicted by the model to decrease HIV-associated morbidity by 10-22% and HIV infections by 9-47% with increasing CD4 threshold for ART initiation. Incremental programme costs were US$2.7-4.4 million higher in the intervention scenarios compared to baseline with higher costs associated with increasing ART initiation criteria; ART accounted for 48-87% of total costs. Across all ART initiation thresholds, ICERs were US$1340, $1090, $1150 and $1360 per DALY averted at ≤200, ≤350, ≤500 cells/mm³ and universal ART access, respectively.

Interpretation: Increases in HIV testing and linkage to care following community-based HTC propagate into population-level health outcomes. The ICERS are <20% of GDP per capita in South Africa and therefore considered very cost-effective. Home HTC should be considered a viable means by which programs can achieve ambitious new targets for HIV treatment.
Editor’s notes: HIV testing and linkage to care are essential to prevent future morbidity and mortality. There has been effort recently to increase access to facility-based HIV testing and counselling, for example through integrated provider-initiated counselling and testing. However, these have not achieved the coverage necessary to meet the UNAIDS 90-90-90 target, which aims to have 90% of all people living with HIV to know their status, 90% of all people diagnosed with HIV receiving sustained antiretroviral therapy, and 90% of all people receiving ART with viral suppression by 2020. A growing body of literature indicates that community-based HIV testing and counselling (HTC) for HIV achieves high testing coverage and linkage to care. However it has previously been warned that the cost-effectiveness of such strategies must be considered before such a programme was implemented.

This modelling analysis evaluates the cost-effectiveness of a community-based package of HIV testing and counselling and linkage to care services. The package includes home-based HTC, together with community mobilization and sensitization, point-of-care CD4 testing, screening for clinical indicators for ART initiation, and follow-up visits by a community health worker to support ART uptake and adherence. The model uses high quality primary cost data, paired with a detailed HIV transmission model. The study finds this package highly cost-effective, with the most costly scenario only $1360 per DALY averted (14 to 19% of GDP), and the least costly scenario $310 per DALY averted.

This study adds to a growing body of literature supporting community-based HTC as a viable means of expanding access to HIV diagnosis and care. These results should encourage policy makers to begin considering community-based HTC as a cost-effective way to meet the ambitious new targets for HIV testing and treatment.

The impact of social services interventions in developing countries: a review of the evidence of impact on clinical outcomes in people living with HIV.


Background: Social service interventions have been implemented in many countries to help people living with HIV (PLHIV) and household members cope with economic burden as a result of reduced earning or increased spending on health care. However, the evidence for specific interventions-economic strengthening and legal services-on key health outcomes has not been appraised.

Methods: We searched electronic databases from January 1995 to May 2014 and reviewed relevant literature from resource-limited settings on the impact of social service interventions on mortality, morbidity, retention in HIV care, quality of life, and ongoing HIV transmission and their cost-effectiveness.

Results: Of 1685 citations, 8 articles reported the health impact of economic strengthening interventions among PLHIV in resource-limited settings. None reported on legal services. Six of the 8 studies were conducted in sub-Saharan Africa: 1 reported on all 5 outcomes and 2 reported on 4 and 2 outcomes, respectively. The remaining 5 reported on 1 outcome each. Seven studies reported on quality of life. Although all studies reported some association between economic strengthening interventions and HIV care outcomes, the quality of evidence was rated fair or poor because studies were of low research rigor (observational or qualitative), had small sample size, or had other limitations. The expected impact of economic strengthening interventions was rated as high for quality of life but uncertain for all the other outcomes.
Conclusions: Implementation of economic strengthening interventions is expected to have a high impact on the quality of life for PLHIV but uncertain impact on mortality, morbidity, retention in care, and HIV transmission. More rigorous research is needed to explore the impact of more targeted intervention components on health outcomes.

Abstract access

Editor’s notes: To mitigate the impact of HIV on people living with HIV and their households, economic strengthening programmes and legal services have often been implemented. However, few have been rigorously evaluated in terms of their impact on HIV outcomes. This review of the literature reveals a limited and weak evidence base on the impact of such social services programmes for people living with HIV on mortality, morbidity, retention in HIV care, quality of life, and ongoing HIV transmission. It only identifies eight studies, all of them on economic strengthening activities, and most of them qualitative or observational in design. The authors conclude that the evidence suggests a high impact of such programmes on the quality of life for people living with HIV, which was consistently reported in the studies identified. Access to other confounding services, such as ART and broader community-based support, requires these findings to be interpreted with caution.

The study clearly highlights the need for more rigorous impact and economic evaluations in this area. Indeed, the review did not identify any studies considering costs or cost-effectiveness. The authors also recommend more research into the feasibility and sustainability of these programmes, as well as greater focus of the implemented programmes on population groups in the greatest need.

7. Eliminate gender inequalities

The case for addressing gender and power in sexuality and HIV education: a comprehensive review of evaluation studies.


Context: Curriculum-based sexuality and HIV education is a mainstay of interventions to prevent STIs, HIV and unintended pregnancy among young people. Evidence links traditional gender norms, unequal power in sexual relationships and intimate partner violence with negative sexual and reproductive health outcomes. However, little attention has been paid to analyzing whether addressing gender and power in sexuality education curricula is associated with better outcomes.

Methods: To explore whether the inclusion of content on gender and power matters for program efficacy, electronic and hand searches were conducted to identify rigorous sexuality and HIV education evaluations from developed and developing countries published between 1990 and 2012. Intervention and study design characteristics of the included interventions were disaggregated by whether they addressed issues of gender and power.

Results: Of the 22 interventions that met the inclusion criteria, 10 addressed gender or power, and 12 did not. The programs that addressed gender or power were five times as likely to be effective as those that did not; fully 80% of them were associated with a significantly lower rate of STIs or unintended pregnancy. In contrast, among the programs that did not address gender or power, only 17% had such an association.

Conclusions: Addressing gender and power should be considered a key characteristic of effective sexuality and HIV education programs.
Abstract Full-text [free] access

Editor’s notes: Curriculum-based sexuality and HIV education plays a central role in the prevention of sexually transmitted infections (STI), HIV and unintended pregnancy among young people. This paper synthesizes current evidence from 22 rigorous evaluation studies that assessed the impacts of different curricula based programmes on HIV, STI or pregnancy risk. The nearly opposite outcomes of programmes that address gender and power compared to those that do not, was striking, with programmes that addressed gender or power being five times as likely to be effective as those that did not.

Several common characteristics of effective programmes were identified. In addition to having interactive and learner-centered pedagogical approaches, effective programmes tended to give explicit attention to gender or power in relationships. Effective programmes fostered critical thinking about how gender norms or inequalities in power manifest and operate and influence life, sexual relationships or health. The programmes also support participants to value themselves and recognize their ability to effect change in their life, relationship or community.

The review findings are consistent with broader theory and evidence that links gender, power and intimate partner violence with sexual and reproductive health outcomes, including HIV. The findings illustrate the value of addressing gender in sexual health programming, illustrating that this is not a luxury for programmes, but rather a critical component of successful programming.

8. Strengthening HIV integration

The impact of water, sanitation, and hygiene interventions on the health and well-being of people living with HIV: a systematic review.


Background: Access to improved water supply and sanitation is poor in low-income and middle-income countries. Persons living with HIV/AIDS (PLHIV) experience more severe diarrhea, hospitalizations, and deaths from diarrhea because of waterborne pathogens than immunocompetent populations, even when on antiretroviral therapy (ART).

Methods: We examined the existing literature on the impact of water, sanitation, and hygiene (WASH) interventions on PLHIV for these outcomes: (1) mortality, (2) morbidity, (3) retention in HIV care, (4) quality of life, and (5) prevention of ongoing HIV transmission. Cost-effectiveness was also assessed. Relevant abstracts and articles were gathered, reviewed, and prioritized by thematic outcomes of interest. Articles meeting inclusion criteria were summarized in a grid for comparison.

Results: We reviewed 3355 citations, evaluated 132 abstracts, and read 33 articles. The majority of the 16 included articles focused on morbidity, with less emphasis on mortality. Contaminated water, lack of sanitation, and poor hygienic practices in homes of PLHIV increase the risk of diarrhea, which can result in increased viral load, decreased CD4 counts, and reduced absorption of nutrients and antiretroviral medication. We found WASH programming, particularly water supply, household water treatment, and hygiene interventions, reduced morbidity. Data were inconclusive on mortality. Research gaps remain in retention in care, quality of life, and prevention of ongoing HIV transmission. Compared with the standard threshold of 3 times GDP per capita, WASH interventions were cost-effective, particularly when incorporated into complementary programs.
Conclusions: Although research is required to address behavioral aspects, evidence supports that WASH programming is beneficial for PLHIV.

Abstract access

Editor’s notes: Researchers, implementers, and policy makers have been examining how to better integrate programmes with overlapping burdens of morbidity and mortality. This paper illustrates how access to clean water and good sanitation practices, or lack thereof, can impact the health of people living with HIV. Water, sanitation, and hygiene (WASH) programmes can improve the negative effects poor water quality and bad sanitation have on people living with HIV. They reduce or even eliminate diarrheal infections, which allow for better absorption of HIV treatment medication that leads to a reduction in viral load and increased CD4 counts. While this systematic review revealed evidence on the reduced burden of morbidity that WASH programmes can confer, little has been done in the way of research linking WASH programmes to mortality in people living with HIV, nor how they may affect adherence or retention in care. Side effects of HIV treatment is a common reason why people stop taking medications, and common side effects are nausea and diarrhoea. It is possible that intestinal issues caused by unsafe drinking water could exacerbate the impact of side effects on people already experiencing them, therefore reducing motivation to continue taking their ARVs. This paper also suggests that synergies in cost sharing and increasing cost effectiveness could be achieved by integrating programmes. However further research is necessary to fully understand the logistical and cost implications.